Spinally-injured rats developed a chronic pain syndrome, including marked mechanical and cold allodynia. The rats were injured 3-6 months before the beginning of the experiment.
Each of the groups of rats were i.p. treated daily for 10 day, respectively, with 60 mg/kg (167,2 µmole/Kg) of NO-gabapentin and with 30 mg/Kg (175 µmole/Kg) of gabapentin. Controls (two groups) received only the vehicle. Each day the treatment of the animals was made at the same time. During the experiment vocalized thresholds to graded mechanical touch/pressure were tested with von Frey hairs.

During testing, rats were gently restrained in a standing position and the von Frey hair was pushed onto the skin until filament becomes bent. The frequency of stimulation was about 1/s and repeated 5-10 times. The intensity of stimulation (g) which induced consistent vocalization (> 75% response rate) is considered as pain threshold. Behavioral testings were carried out before the daily for the control group and 1 hour after administration for the treated groups.

The effect of chronic daily administration of gabapentin and NO-gabapentin is reported in Table 6.
NO- gabapentin alleviated mechanical allodynia following the first administration and a significant effect was maintained up to day 6. Gabapentin did not produce a significant effect up to the second day and the effect was lower than that of NO-gabapentin.

Table 1

| Evaluation of the analgesic activity of gabapentin and of the NO-gabapentin derivative in the experiment F1 (rats injected in a paw with formalin) | | |
|---|---|---|
| Treatment | Dose (mg/kg) | Number "paw licking" % |
| Controls | | 100 |
| Gabapentin | 90 | 80 |
| NO-Gabapentin | 50 | 70 |

Table 2

| Ex. F2 :analgesic activity of the drugs used in the chronic (neuropathic) pain treatment in combination with a nitric oxide-donor drug | |
|---|---|
| Treatment | response % |
| Controls | 100 |
| Clomipramine | 72 |
| NO-ASA | 82 |
| Clomipramine + NO-ASA | 29 |

Table 3

| Rex. F3 : acute toxicity of gabapentin and NO-gabapentin in diabetic rats | |
|---|---|
| Treatment | lethality % |
| Controls | 10 |
| Gabapentin | 50 |
| NO-gabapentin | 20 |

Table 4

| Ex. F4 : effect of different doses of NO-gabapentin and gabapentin on cold stimulation in a rat model of neuropathic pain. Response is evaluated with by a score (0-3). | | | | | |
|---|---|---|---|---|---|
| Compound | Dose (µmole/kg) | Time (min) | | | |
| | | 0 | 30 | 120 | 240 |
| Control | - | 2 | 2 | 2 | 2 |
| NO-gabapentin | 55.7 | 2 | 2 | 2 | - |
| NO-gabapentin | 167.2 | 2 | 1 | 1 | - |
| NO-gabapentin | 278.7 | 2 | 1 | 1 | 1 |
| Gabapentin | 175 | 2 | 2 | 2 | 2 |
| gabapentin | 584 | - | - | - | - |

Table 5

| Ex. F4 :effect of different acute doses of NO-gabapentin and gabapentin on motor performance in a rat model of *neuropathic pain*. | | | | | |
|---|---|---|---|---|---|
| Compound | Dose (µmole/kg) | Time (min) | | | |
| | | 0 | 30 | 120 | 240 |
| Control | - | 15 | 15 | 15 | 15 |
| NO-gabapentin | 55.7 | 14 | 14 | 14 | - |
| NO-gabapentin | 167.2 | 14 | 14 | 15 | - |
| NO-gabapentin | 278.7 | 14 | 15 | 14 | 14 |
| Gabapentin | 175 | 20 | 20 | 20 | 20 |
| Gabapentin | 584 | 15 | 30 | 30 | 25 |

Table 6

| Ex. F5 :effect of repeated administration of NO-gabapentin and gabapentin on vocalization threshold (g) to mechanical stimulation with von Frey hairs in a rat model of neuropathic pain. | | | | | |
|---|---|---|---|---|---|
| Compound | Dose (µmole/kg) | Day | | | |
| | | 1 | 2 | 4 | 6 |
| Baseline | - | 2 | 5 | 8 | 2 |
| NO-gabapentin | 167.2 | 100 | 200 | 400 | 90 |
| Baseline | - | 5 | 3 | 3 | 5 |
| Gabapentin | 175 | 5 | 6 | 70 | 90 |

CLAIMS

1. Nitrooxyderivative compounds or salts thereof having the following general formula (I):

$$A\text{-}(B)_{b0}\text{-}(C)_{c0}\text{-}NO_2 \qquad (I)$$

wherein:

c0 is an integer and is 0 or 1, preferably 1;

b0 is an integer and is 0 or 1, with the proviso that c0 and b0 cannot be contemporaneously equal to zero;

A = R-$T_1$-, wherein R is the radical of an analgesic drug for the chronic pain, in particular for the neuropathic pain;

$T_1$ = $(CO)_t$ or $(X)_{t'}$, wherein X = O, S, $NR_{1C}$, $R_{1C}$ is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = -$T_B$-$X_2$-$T_{BI}$- wherein

$T_B$ and $T_{BI}$ are equal or different;

$T_B$ = (CO) when t = 0, $T_B$ = X when t' = 0, X being as above;

$T_{BI}$ = $(CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0; and tx = 0 when txx = 1; X is as above;

$X_2$, bivalent radical, is such that the corresponding precursor of B -$T_B$-$X_2$-$T_{BI}$- wherein the free valences of $T_B$ and of $T_{BI}$ are saturated each with OZ, with Z or with -$N(Z^I)(Z^{II})$, being:

Z = H, $C_1$-$C_{10}$, preferably $C_1$-$C_5$ alkyl linear or branched when possible,

$Z^I$, $Z^{II}$ equal to or different have the values of Z as above, depending on that $T_B$ and/or $T_{BI}$ = CO or X, in function of the values of t, t', tx and txx;

the precursor compound of B as above defined being selected from the following classes of compounds:

- aminoacids, selected from the following: L-carnosine, anserine, selenocysteine, seleno-methionine, penicillamine, N-acetylpenicillamine, cysteine, N-acetylcysteine, glutathione or esters thereof, preferably ethyl or isopropyl ester;
- hydroxyacids, selected from the following: gallic acid, ferulic acid, gentisic acid, citric acid, caffeic, dihydrocaffeic acid, p-cumaric acid, vanillic acid;
- aromatic and heterocyclic polyalcohols, selected from the following: nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulfurethyne, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzylthio glycolate, p-cumaric alcohol, 4-hydroxy-phenylethyl alcohol, coniferyl alcohol, allopurinol;
- compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid, fumaric acid, dihydroxymaleic acid, edetic acid;

C = bivalent radical $-T_c-Y-$ wherein

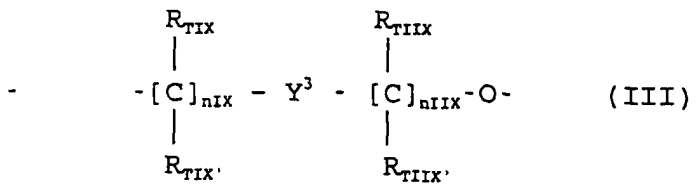
when b0 = c0 = 1: $T_c$ = (CO) when tx = 0, $T_c$ = X when txx = 0, X being as above defined,

when b0 = 0 : $T_c$ = (CO) when t = 0, $T_c$ = X when t' = 0, X being as above defined,

when c0 = 0 : tx = 0, $T_{BI}$ = X = —O—;

Y has one of the following meanings:

$Y_p$:



(III)

wherein:

nIX is an integer from 0 to 5, preferably 1;

nIIX is an integer from 1 to 5 preferably 1;

$R_{TIX}$, $R_{TIX'}$, $R_{TIIX}$, $R_{TIIX'}$, equal to or different from each other are H or linear or branched $C_1$-$C_4$ alkyl; preferably $R_{TIX}$, $R_{TIX'}$, $R_{TIIX}$, $R_{TIIX'}$ are H;

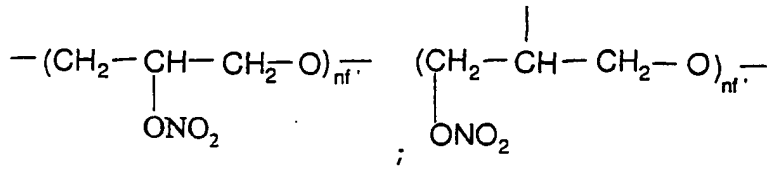
$Y^3$ is a saturated, unsaturated or aromatic heterocyclic ring, having 5 or 6 atoms, containing from one to three heteroatoms, preferably from one to two, said heteroatoms being equal or different and selected from nitrogen, oxygen, sulphur;

or Y can be:

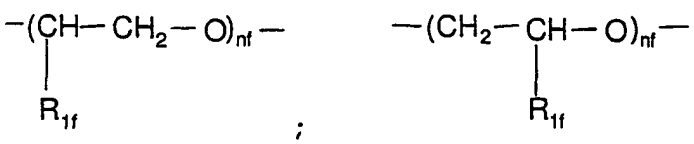
$Y_o$, selected from the following:

an alkylenoxy group R'O wherein R' is a linear or branched when possible $C_1$-$C_{20}$, having preferably from 2 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above;

or Y is selected from one of the following groups:

- 
;

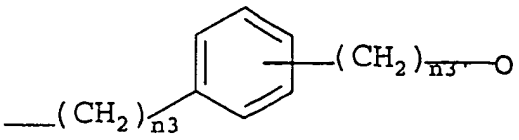
wherein nf' is an integer from 1 to 6 preferably from 1 to 4;

- 
;

wherein $R_{1f}$ = H, $CH_3$ and nf is an integer from 1 to 6; preferably from 2 to 4;

$Y_{AR}$, selected from:

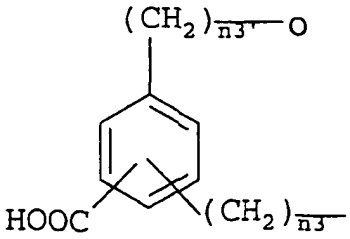
$Y_{AR1}$:



(V)

wherein n3 is an integer from 0 to 5 and n3' is an integer from 1 to 3; or

$Y_{AR2}$:

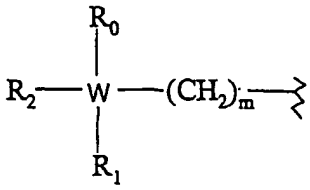


(VI)

wherein n3 and n3' have the above meaning.

2. Compounds according to claim 1, wherein the radical R is that of chronic analgesic drugs, in particular of drugs for the neuropathic pain.

3. Compounds according to claims 1-2, wherein R is the radical of an analgesic drug, having formula II:



(II)

wherein:

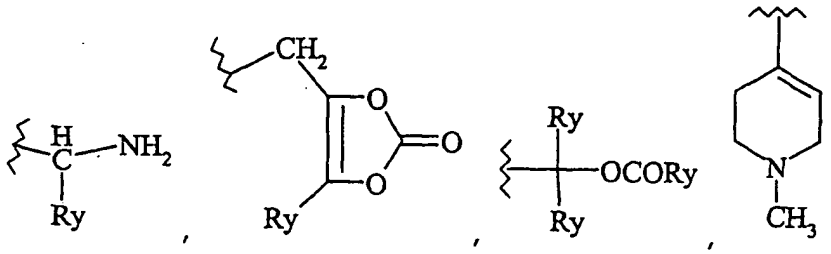
W is a carbon atom or a nitrogen atom;

m is an integer from 0 to 2;

$R_0$ = H, $-(CH_2)_n-NHR_{1A}$, n being an integer from 0 to 2, wherein

$R_{1A}$ = H, $-C(O)-R_{1H}$, $-C(O)O-R_{1H}$, wherein

$R_{1H}$ is a linear or branched $C_1-C_{10}$ alkyl, a phenyl or benzyl group; or $R_{1H}$ has one of the following meanings:



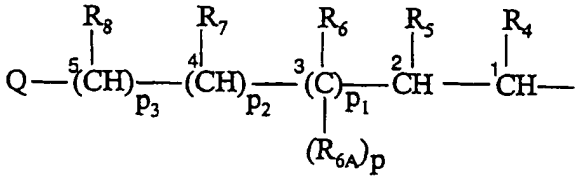
(II-B) (II-C) (II-D) (II-E)

wherein Ry is hydrogen, a linear or branched $C_1-C_{10}$ alkyl, a phenyl or benzyl group;

$R_1$ = H, when W = N, $R_1$ is the electronic doublet on the nitrogen atom (free valence);

$R_2$ is chosen between the following groups:

- phenyl, optionally substituted with an halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;
- mono- or di-hydroxy substituted benzyl, preferably 3-4 di-hydroxy substituted benzyl;
- amidino group: $H_2N(C=NH)-$;
- the radical of formula (IIA), wherein optionally one unsaturation of ethylene type can be present between the carbon atoms in position 1 and 2, or 3 and 4, or 4 and 5:



(IIA)

*wherein:*

p, $p_1$, $p_2$ are integers, equal to or different from each other and are 0 or 1;

$p_3$ is an integer from 0 to 10;

$R_4$ is hydrogen, linear or branched $C_1$-$C_6$ alkyl, free valence;

$R_5$ can have the following meanings:

- linear or branched $C_1$-$C_6$ alkyl,
- $C_3$-$C_6$ cycloalkyl,
- free valence,
- $OR_A$, wherein $R_A$ has the following meanings:

- linear or branched $C_1$-$C_6$ alkyl optionally substituted with one or more halogen atoms, preferably F,
- phenyl, optionally substituted with one halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;

$R_6$, $R_{6A}$, $R_7$, $R_8$, equal or different, are H, methyl; or free valence;

with the proviso that in the radical of formula (IIA) when one unsaturation of ethylene type between $C_1$ and $C_2$ is present, $R_4$ and $R_5$ are free valences such as to form the double bond between $C_1$ and $C_2$; when the unsaturation is between $C_3$ and $C_4$, $R_6$ and $R_7$ are free valences such as to form the double bond between $C_3$ and $C_4$; when the unsaturation is between $C_4$ and $C_5$, $R_7$ and $R_8$ are free valences such as to form the double bond between $C_4$ and $C_5$;

Q is equal to H, OH, $OR_B$ wherein $R_B$ is benzyl, a linear or branched $C_1$-$C_6$ alkyl, optionally substituted with one or more halogen atoms, preferably F, phenyl optionally substituted with one halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;

or Q can have one of the following meanings:

- $C_3$-$C_6$ cycloalkyl;
- linear or branched $C_1$-$C_6$ alkyl;
- guanidine ($H_2NC(=NH)NH-$);
- thioguanidine ($H_2NC(=S)NH-$);

in formula (II) $R_2$ with $R_1$ and with W = C taken together form a $C_4$-$C_{10}$, preferably $C_6$, saturated or unsaturated, preferably saturated, ring.

4. Compounds according to claim 3, wherein:

when in formula (II) W = C, m = 1 and $R_0$ = -$(CH_2)_n$-$NH_2$ with n = 1, $R_2$ and $R_1$ with W as above defined form together the cyclohexane ring, in the radical A of formula (I) $T_1$ = CO and the free valence of A is saturated with OH, the precursor drug of R is known as gabapentine;

when in formula (II) W = C, m = 0 and $R_0$ = -$(CH_2)_n$-$NH_2$ with n = 0, $R_1$ = H, $R_2$ is the radical of formula (IIA) wherein p = $p_1$ = 1, $p_2$ = $p_3$ = 0, $R_4$ = $R_5$ = $R_6$ = $R_{6A}$ = H, Q = H, in the radical A of formula (I) $T_1$ = CO and the free valence of A is saturated with OH, the precursor drug of R is known as norvaline;

when in formula (II) W = C, m = 0 and $R_0$ = -$(CH_2)_n$-$NH_2$ with n = 0, $R_1$ = H, $R_2$ is the radical of formula (IIA) wherein p = $p_1$ = 1, $p_2$ = $p_3$ = 0, $R_4$ = $R_5$ = $R_6$ = $R_{6A}$ = H, Q is the guanidine group, in the radical A of formula (I) $T_1$ = CO and the free valence of A is saturated with OH, the precursor drug of R is known as arginine;

when in formula (II) W = C, m = 0 and $R_0$ = -$(CH_2)_n$-$NH_2$ with n = 0, $R_1$ = H, $R_2$ is the radical of formula (IIA) wherein p = $p_1$ = 1, $p_2$ = $p_3$ = 0, $R_4$ = $R_5$ = $R_6$ = $R_{6A}$ = H, Q is the thioguanidine group, in the radical A of formula (I) $T_1$ = CO and the free valence of A is saturated with OH, the precursor drug of R is known as thiocitrulline;

when in formula (II) W = C, m = 1 and $R_0$ = -$(CH_2)_n$-$NH_2$ with n = 1, $R_1$ = H, $R_2$ is the radical of formula (IIA) wherein p = $p_1$ = $p_2$ = $p_3$ = 0, $R_4$ = H, $R_5$ = Q = $CH_3$, in the

radical A of formula (I) $T_1$ = CO and the free valence of A is saturated with OH, the precursor drug of R is known as pregabaline;

when in formula (II) W = C and has configuration (S), m = 1 and $R_0$ = $-(CH_2)_n-NH_2$ with n = 1, $R_1$ = H, $R_2$ is the radical of formula (IIA) wherein p = $p_1$ = $p_2$ = $p_3$ = 0, $R_4$ = H, $R_5$ = Q = $CH_3$, in the radical A of formula (I) $T_1$ = CO and the free valence of A is saturated with OH, the precursor drug of R is known as (S)3-isobutylGABA;

when in formula (II) W = C, m = 1 and $R_0$ = $R_1$ = H, $R_2$ is the radical of formula (IIA) wherein p = $p_1$ = 1, $p_2$ = $p_3$ = 0, $R_4$ = $R_5$ = $R_6$ = $R_{6A}$ = H, Q is the guanidine group, in the radical A of formula (I) $T_1$ = NH and the free valence of A is saturated with H, the precursor drug of R is known as agmatine;

when in formula (II) W = C, m = 2 and $R_0$ = $-(CH_2)_n-NH_2$ with n = 0, $R_1$ = H, $R_2$ is the radical of formula (IIA) wherein p = $p_1$ = $p_2$ = $p_3$ = 0, $R_4$ and $R_5$ are free valences and between $C_1$ and $C_2$ there is one ethylene unsaturation, Q = H, in the radical A of formula (I) $T_1$ = CO and the free valence of A is saturated with OH, the percursor drug of R is known as vigabatrin;

when in formula (II) W = C m = 0 and $R_0$ = $-(CH_2)_n-NH_2$ with n = 0, $R_1$ = H, $R_2$ is the radical 3-4 di-hydroxy substituted benzyl, $T_1$ = CO and the free valence of A is saturated with OH, the percursor drug of R is known as 2-amino-3-(3,4-dihydroxyphenyl)propanoic acid (dopa).

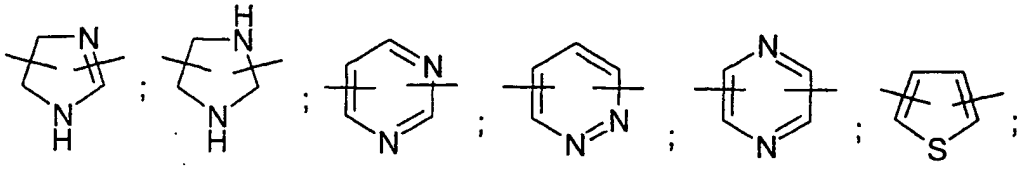
5. Compounds according to claims 1-2, wherein the precursors of A = R-$T_1$ in formula (I) are lamotrigine, topiramate, tiagabine, zonisamide, carbamazepine, felbamate,

amineptine, amoxapine, demexiptiline, desipramine, nortriptyline, opipramol, tianeptine.

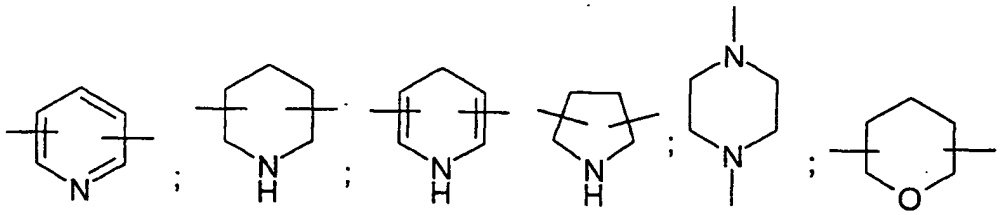
6. Compounds according to claims 1-5, wherein when in formula (I) b0 = 0, Y in the bivalent linking group C is selected between $Y_P$ and $Y_{AR}$ as above defined.

7. Compounds according to claim 6, wherein $Y^3$ is selected from the following bivalent radicals:

(Y1) (Y2) (Y3) (Y4) (Y5) (Y6) (Y19)



(Y7) (Y8) (Y9) (Y10) (Y11) (Y18)



(Y12) (Y13) (Y14) (Y15) (Y16) (Y17)

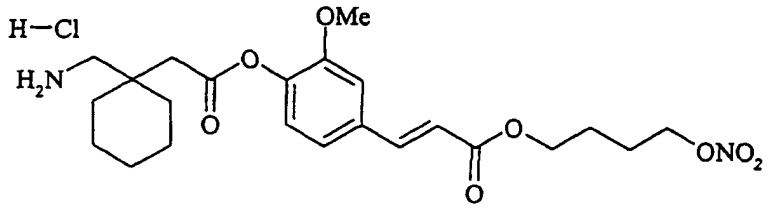
8. Compounds according to claim 7, wherin $Y^3$ is selected from (Y12), having the two free valences in the ortho positions with respect to the nitrogen atom; (Y16) with the two valences linked to the two heteroatoms, Y1 (pyrazol) 3,5-disubstituted, (Y19) wherein the free valence on the ring is found in para position to the nitrogen atom.

9. Compounds according to claims 1-8, wherein in formula (I) the precursors of B are the following: ferulic acid, N-acetylcysteine, cysteine, caffeic acid, hydro-caffeic and gentisic acid.

10. Compounds according to claims 1-9, wherein the precursor drugs are selected from gabapentine, norvaline, arginine, pregabaline, (S)3-isobutylGABA, agmatine.

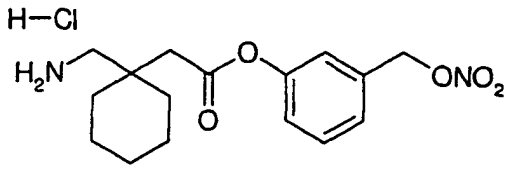
11. Compounds according to claims 1-10, selected from the following:

1-(aminomethyl)cyclohexan acetic acid 2-methoxy -4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XV)



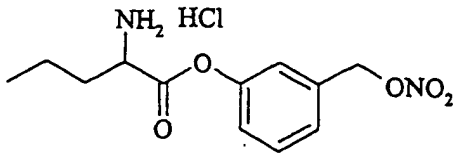

(XV)

1-(aminomethyl)cyclohexan acetic acid 3-(nitro-oxymethyl) phenyl hydrochloride ester (XVI)



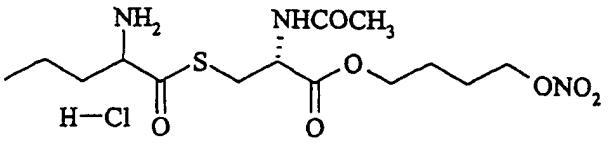

(XVI)

2-aminopentanoic acid 3-(nitrooxymethyl)phenyl hydrochloride ester (XVII)



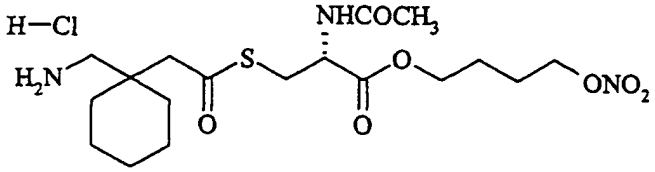
(XVII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 2-amino hydrochloride pentanoate (XVIII)



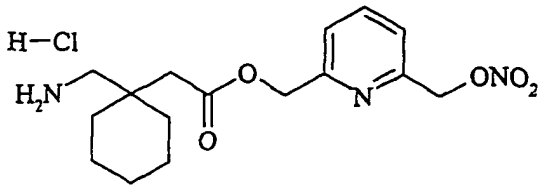
(XVIII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 1-(aminomethyl)cyclohexanacetate hydrochloride (XIX)



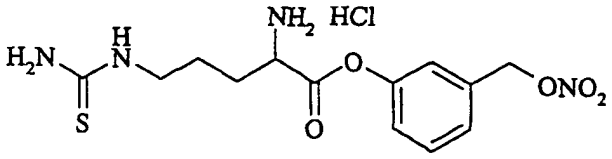
(XIX)

1-(aminomethyl)cyclohexanacetic acid-, [6-(nitrooxy methyl)-2-pyridinyl]methyl hydrochloride ester (XX)



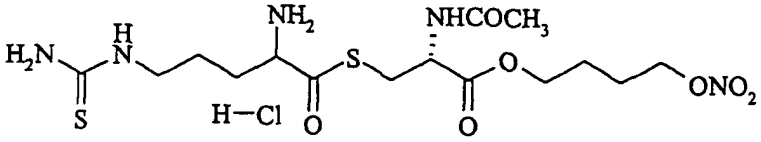
(XX)

alpha-amino-delta-thioureidopentanoic acid, 3-(ni-trooxy methyl)phenyl hydrochloride ester (XXI)



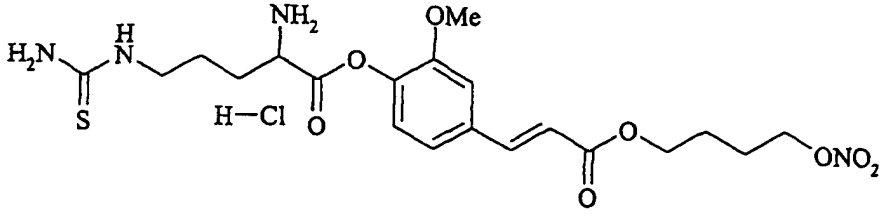
(XXI)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, alpha-amino-delta-thioureidopentanoate hyrochloride (XXII)



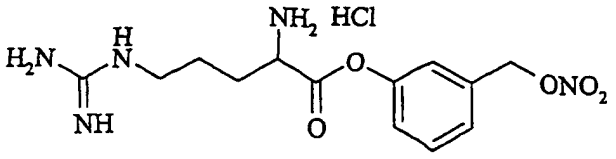
(XXII)

alpha-amino-delta-thioureidopentanoic acid, 2-me-thoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXIII)



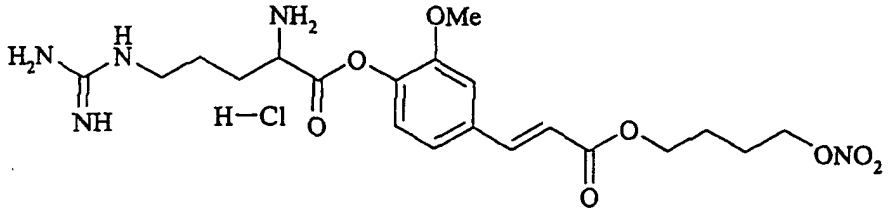
(XXIII)

2-amino-5-guanidinopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXIV)



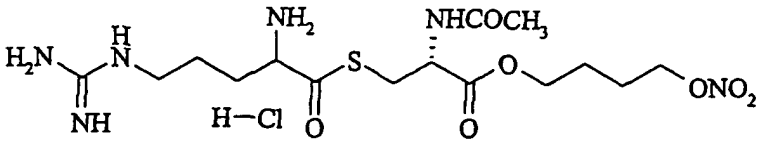
(XXIV)

2-amino-5-guanidinopentanoic acid-, 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXV)



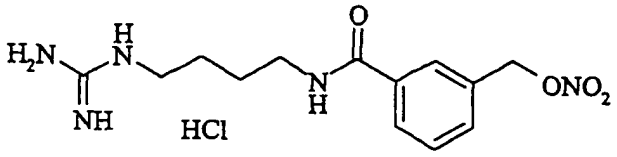
(XXV)

(S)-N-acetylcysteine-4-(nitrooxy)butyl ester, 2-amino-5-guanidinopentanoate hydrochloride (XXVI)



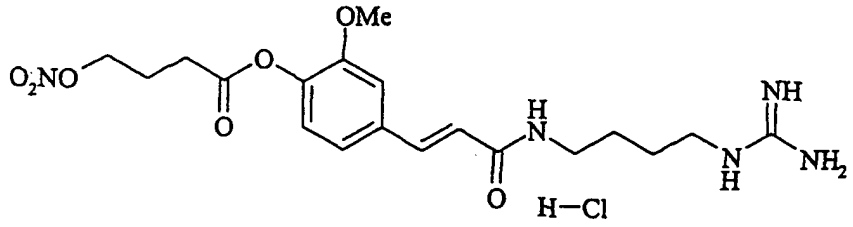
(XXVI)

4-(guanidine)butyl-3-nitrooxymethylbenzamide (XXVII)



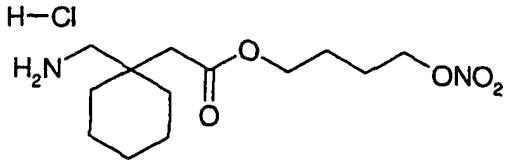
(XXVII)

4-(guanidine)butyl-3-[4-(4'-nitrooxybutyryloxy)-3-(methoxy)]phenyl-2-propenamide chloride (XXVIII)



(XXVIII)

1-(aminomethyl)cyclohexan acetic acid 4-(nitroxy) butyl hydrochloride ester (XXIX)



(XXIX)

12. Compounds according to claims 1-11, as nitrate salts.
13. Compounds according to claims 1-12, in combination with NO-donor compounds.
14. Compounds according to claim 13, wherein the NO donor compounds contain in the molecule radicals of drugs belonging to the classes of aspirin, ibuprofen, paracetamol, naproxen, diclofenac, flurbiprofen.

15. Analgesic drugs for the treatment of the chronic pain, in particular the neuropathic pain, in combination with NO donor compounds.

16. Analgesic drugs according to claim 15, wherein the drug is selected from the following: lamotrigine, topiramate, tiagabime, zonisamide, carbamazepine, felbamate, amineptine, amoxapine, demexiptiline, desipramine, nortriptyline, opipramol, tianeptine, ami-triptyline, butriptyline, clomipramine, dibenzepin, dimetacrine, dothiepin, doxepin, fluacizine, imipramine, iprindole, lofepramine, melitracen, noxiptilin, propi-zepine, protriptyline, trimipramine.

17. Pharmaceutical compositions for parenteral, oral and topical use, comprising the compounds according to claims 1-16.

18. Compounds according to claims 1-17, for use as medicament.

19. Use of the compounds according to claims 1-17, for preparing drugs for the chronic pain, in particular the neuropathic pain.

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(54) Title: NITRODERIVATIVES AS DRUGS FOR DISEASES HAVING AN INFLAMMATORY BASIS

(57) Abstract: Use for the treatment of diseases having an inflammatory basis of compounds or salts thereof, having the following general formula (I): $A\text{-}X_1\text{-}L\text{-}(W)_p\text{-}NO_2$ wherein A contains the radical of a drug, $X_1$ and W are bivalent radicals, L is a covalent bond or oxygen, sulphur, $NR_{1c}$ wherein $R_{1c}$ is H or a $C_1\text{-}C_5$ linear or branched alkyl.